

March 1, 2007

Dr. William Stott  
Technical Contact  
The Dow Chemical Company  
1691 North Swede  
Midlands, MI 48674

Dear Dr. Stott:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 2-Nitropropane, posted on the ChemRTK HPV Challenge Program Web site on June 3, 2005. I commend The Dow Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Dow Chemical advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: [oppt.ncic@epa.gov](mailto:oppt.ncic@epa.gov) and [chem.rtk@epa.gov](mailto:chem.rtk@epa.gov).

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at [tsc hotline@epa.gov](mailto:tsc hotline@epa.gov).

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark W. Townsend, Chief  
HPV Chemicals Branch

Enclosure

cc: O. Hernandez  
C. Augustyniak  
J. Willis

**EPA Comments on Chemical RTK HPV Challenge Submission:  
2-Nitropropane**

**Summary of EPA Comments**

The sponsor, Dow Chemical Company, submitted a test plan and robust summaries to EPA for 2-Nitropropane (2-NP, CAS No. 79-46-9) dated May 13, 2005. EPA posted the submission on the ChemRTK HPV Challenge Web site on June 3, 2005.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.
2. Environmental Fate. Adequate data were submitted for these endpoints for the purposes of the HPV Challenge Program. However, the submitter needs to revise the concluding statements in the Transport between Environmental Compartments section of the robust summaries.
3. Health Effects. The submitter needs to provide adequate data for the developmental toxicity endpoint. EPA reserves judgement on the claim for closed system intermediate and reduced testing status pending the submission of more information. If this information is unavailable, EPA suggests that the submitter provide data for the reproductive toxicity endpoint using a combined reproductive/developmental toxicity screening test (OECD TG 421) to satisfy both the reproductive and developmental toxicity endpoints. The submitter also needs to address deficiencies/discrepancies in the robust summaries.
4. Ecological Effects. EPA reserves judgment on the fish toxicity endpoint pending verification of the analytical monitoring method. EPA disagrees with the submitter that adequate data exist for the aquatic invertebrate and algal toxicity endpoints. Therefore, the submitter needs to provide adequate acute toxicity data for the aquatic invertebrate and algal toxicity endpoints.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

### **EPA Comments on the 2-Nitropropane Challenge Submission**

#### **Test Plan**

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Adequate data were submitted for all endpoints for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data for acute, genetic and repeated-dose toxicity are adequate for the purposes of the HPV Challenge Program. However, the submitter needs to address deficiencies and discrepancies in the robust summaries.

*Acute Toxicity.* The submitter is proposing additional acute oral toxicity testing. However, EPA considers this endpoint addressed by an adequate acute inhalation toxicity study. In addition, limited information, although of low reliability, is available on acute oral toxicity.

*Repeated-Dose Toxicity.* Several repeated-dose inhalation toxicity studies are available, but just three studies (Ref. 35/36, rat and rabbit; 37/38, rat; and 39/40, rat), considered together, adequately address the endpoint for the purposes of the HPV Challenge Program. The submitter needs to include the missing details for these studies in the robust summaries.

*Genetic Toxicity (Gene Mutations).* Data from three positive *in vitro* microbial mutagenicity assays (Ames Tests-Ref. 45, 46, 47) have various deficiencies, but when considered together address the endpoint for the purposes of the HPV Challenge Program. However, the submitter needs to include the missing study details in the robust summaries.

*Genetic Toxicity (Chromosomal Aberrations).* Data from three chromosomal aberration studies (negative bone marrow micronucleus assays in rats and mice and a positive hepatocyte micronucleus assay in rats) are adequate to address the endpoint for the purposes of the HPV Challenge Program. The submitter, however, needs to include missing study details in the robust summaries.

*Reproductive Toxicity.* The submitter indicated that the reproductive toxicity endpoint is satisfied by the histological evaluation of reproductive organs (prostate, seminal vesicle, testis, uterus, and ovary) in a 22-month repeated-dose inhalation toxicity study in rats. However, histological evaluation of reproductive organs with negative results from the repeated-dose toxicity study will satisfy this endpoint only when adequate developmental toxicity data with negative results are available. Because the submitted data for the developmental toxicity endpoint are inadequate (see discussion of this endpoint below), the reproductive toxicity endpoint remains unaddressed for the purposes of the HPV Challenge Program. The submitted data for a dominant lethal test do not adequately address this endpoint.

The submitter also claims an exemption from reproductive toxicity testing on the basis that 2-nitropropane is a site-limited, closed system intermediate. The Guidance for Testing Closed System Intermediates for the Challenge Program (<http://www.epa.gov/chemrtk/pubs/general/closed9.htm>) allows for a reduced testing protocol provided certain criteria are met. The information required to judge a “closed-system intermediate” claim must address the following:

I. Site information

- A. Number of sites.
- B. Basis for “closed process” conclusion at each site.
  - 1) Process description.
  - 2) Monitoring data showing no detection.
  - 3) In the absence of monitoring data, the basis for believing that releases do not occur.
- C. Data on “presence in distributed products.”

II. Information on transport (mode, volume, controls, etc.)

III. A data search showing that the chemical is not present in other end products.

The information provided by the submitter is not adequate to satisfy the closed system intermediate criteria. The following information is needed to support this claim:

I.B. *Basis for closed process conclusion at each site:* The submitter needs to show that sampling, material transfers, and use as a taggant are conducted in closed systems; the information provided is insufficient to document that the subject chemical is managed in closed systems at all sites.

I.B.2). *Monitoring data, if available, showing no detection in any media:* Although the statements in the test plan indicate that the subject chemical is handled in a careful manner, the information is insufficient to conclude that monitoring would not detect the subject chemical.

II. *If transport occurs, information on the mode of transport, volume, type of consignment, and controls during transport and transfer at dispatching and receiving sites:* The subject chemical is transported by piping, drums, and in bulk (rail and marine transport) and the test plan indicates exposure to the subject chemical is most likely to occur during material transfers. The submitter needs to provide information on controls during transfer at dispatching and receiving sites.

III. *Data on presence in distributed product or the basis for believing it is not present; Supporting evidence that the chemical is not present in other end-products:* The chemical is used as a taggant in C-4 production and in laboratories for research and development. The subsequent disposition of the C-4 product is not discussed. Because the C-4 product contains 2-nitropropane, the information is insufficient to document that 2-nitropropane is not present in any distributed product or any other end-product. According to the test plan, the submitter is unaware of any consumer applications of 2-nitropropane.

EPA therefore reserves judgment on whether 2-nitropropane meets the criteria for a “closed system intermediate” pending the submission of additional information. If this information is unavailable, EPA suggests that the submitter provide data for the reproductive toxicity endpoint using a combined reproductive/developmental toxicity screening test (OECD TG 421) to satisfy the reproductive and developmental toxicity endpoints (see next paragraph).

*Developmental Toxicity.* The submitted data are inadequate to satisfy the endpoint because the route of administration was intraperitoneal and no maternal toxicity occurred at the only dose tested. The submitter needs to provide adequate data for the developmental toxicity endpoint as described above.

#### Ecological Effects (fish, invertebrates, and algae)

*Fish.* EPA reserves judgment on the adequacy of the data submitted for this endpoint pending the submission of additional information on the analytical monitoring method. If this information is unavailable, then the submitter needs to provide data for this endpoint according to OECD TG 203.

*Invertebrates and algae.* EPA disagrees with the submitter that adequate data were submitted for these endpoints. Test conditions did not indicate that adequate steps were taken to prevent loss of the test substance during the tests. Since 2-nitropropane is a volatile chemical with a Henry's Law constant of  $1.25 \times 10^{-4}$  atm-m<sup>3</sup>/mol, the submitter needs to test for these endpoints in a closed system and in accordance with OECD TGs 201 and 202, respectively.

## **Specific Comments on the Robust Summaries**

### **Generic comments**

In general, the robust summaries did not provide all necessary details. Each summary should clearly identify the standardized study guideline, and GLP compliance. Table 1 of the test plan shows that some of the studies were GLP-compliant, but the summaries did not always indicate this. The submitter should consult EPA guidance for the preparation of robust summaries (<https://www.epa.gov/chemrtk/pubs/general/robsumgd.htm>).

### **Environmental Fate**

*Fugacity.* On page 14 (Transport between Environmental Compartments) of the robust summaries, the submitter states that: "If released directly to water, the substance will remain dissolved in water and is expected to be ultimately biodegraded. If released to soil, 2-nitropropane will be primarily dissolved in soil and pore water (groundwater), and is expected to be ultimately biodegraded." The two statements that say ". . .and is expected to be ultimately biodegraded" are speculative and need to be deleted.

### **Health Effects**

*Acute Toxicity.* Details missing from the summary of the acute inhalation toxicity study include the study guideline followed and the purity of the test compound.

*Repeated-Dose Toxicity.* Summaries of three repeated-dose inhalation toxicity studies have various deficiencies (Refs. 35/36, 37/38, and 39/40). Data missing include the test guideline used and whether significant deviations from the guideline occurred. Methodological limitations in the studies include the use of fewer than three test concentrations in each experiment, lack of some biological and histological analyses, and, in one case, potential exposure to a decomposition product. Data from five other studies were not considered owing to significant deviations from OECD test guidelines (e.g., use of animals other than rats, less than recommended number of animals used, and inhalation studies less than 14 days).

*Genetic Toxicity (Gene mutations).* Details missing from the summaries of the mutagenicity assays included specific study guidelines followed, information on GLP compliance, the purity of the compound tested, mean number of revertant colonies, and whether positive and negative controls responded correctly and the number of replicates and incubation conditions.

*Genetic Toxicity (Chromosomal Aberrations).* The robust summaries for the micronucleus assays lacked study details including the specific study guidelines followed and information on GLP compliance. The test compound purity was not clearly stated. The summaries did not indicate if positive control groups were included in the hepatocyte test in rats or the bone marrow test in mice or if appropriate responses occurred in the positive control groups used in the bone marrow test in rats.

### **Followup Activity**

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.